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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,077	07/19/2001	Ashok Arasappan	IN01156	9892

24265 7590 11/26/2003

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,077	ARASAPPAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *39-41* is/are withdrawn from consideration.

5)☒ Claim(s) *43* is/are allowed.

6)☒ Claim(s) *1,7,36-38 and 42-47* is/are rejected.

7)☐ Claim(s) *2-6 and 8-35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicants' election of Group 3 with traverse is acknowledged (claims 1-38, limited to G2 and G3), as is the elected specie.

Applicants have questioned the justification of separating Groups 1, 2 and 4 from Group 3. Applicants have argued that in order for this separation to be justified, Groups 1, 2 and 4 would have to be classified differently from Group 3, or else that a different "field of search" would be required. As it happens, both of these criteria are met. Nevertheless, the restriction may be reconsidered at a later time.

Claims 1-38 and 42-47 are examined in this Office action; claims 39-41 are withdrawn from consideration.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-38, 42, 44-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to pharmaceutical compositions, or to a method of making such.

One or more of the rejected claims also recite that disorders "associated with HCV protease" can be successfully treated by administering the claimed compounds. As it happens, none of these claims is enabled.

Applicants have demonstrated only inhibition of HCV NS3/NS4a serine protease. It is stipulated that such inhibition will occur *in vivo*. But that does not, in and of itself, translate into an effective therapy of a hepatitis infection. A key issue is whether the NS3/NS4a protease can be inhibited to a sufficient degree to cause an actual reduction in population of the virions. Issues such as proper anatomical localization, bioavailability, susceptibility of the claimed compounds to proteases and monooxygenases would have to be addressed. For example, if the virus is replicating at a rate of 100 "units" per day in the absence of the compound, and 90 units per day in the presence of the compound, one could say that inhibition had been achieved. However, if the virus is replicating at a rate of 90 per day in spite of the presence of the compound (of claim 1), the patient's condition will still worsen, and "treatment" will not have been achieved. As it happens, structure/activity relationships are unpredictable. As observed by Tung (WO 98/17679), compounds within that disclosed genus (table 9, pp. 106-107) exhibited more than a 100-fold range of efficacies in the inhibition of HCV NS3 protease. Many of those compounds characterized as exhibiting an inhibition above 100 *micro*molar may have been completely inactive. (See also table I of WO 99/07734). Thus, one question is, can applicants look at a structure and determine its activity, even *in vitro*? And if not, how can applicants make

predictions about what will happen *in vivo*? As stated in Ingallinella (*Biochemistry* **37**, 8906, 1998) at page 8906, col 1:

"Neither an effective therapy for hepatitis C-associated chronic hepatitis nor a vaccine for preventing HCV infection has... been developed.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As it happens, effective treatment of viral infections such as hepatitis cannot be predicted from *in vitro* data alone; undue experimentation would be required to practice the claimed invention. It is suggested that the term "pharmaceutical" be deleted at every occurrence; either of the following could be used:

> *A composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.*
>
> *A composition comprising a pharmaceutically acceptable carrier in combination with a compound of claim 1 in an amount effective to inhibit hepatitis C nonstructural protein-3 protease (HCV NS3 protease)*

If deemed appropriate, the following claim can be added:

> *A method of inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease) comprising administering a compound according to claim 1 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.*

If there is descriptive support for it, the following claim could be added:

> *A method of of inhibiting hepatitis C virus replication comprising administering a compound of claim 1 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.*

*

Claims 7 and 36 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 7, a substituent variable is defined in the last two lines of the claim as follows: "R2' is phenyl... piperidyl **and** pyridyl". Here, it appears that "and" should be - - or - - .

- Claim 36 is drawn to a composition, yet does not require anything to be present other than a single compound. A single compound, however, is not a composition. Thus, the question is, how can it be said that a chemist who is in possession of one single, pure compound is in possession of a composition? It is suggested that claim 36 be amended to require the presence of a second component, such as a carrier.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another

filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. §102(e) as being anticipated by Dressen (USP 6,407,066).

Dressen discloses (col 17, lines 35-44) a compound which is encompassed by the instant claims when the substituent variables are as follows:

R^1 = -COOH

G = hydrogen

R^2 = alkylaryl; and

$Y(R^4)(Z)CH(R^3)X$ represents benzyloxycarbonyl.

Thus, the claim is anticipated.

*

Claim 1 is rejected under 35 U.S.C. §102(b) as being anticipated by Shiba, Tetsuo (*Bulletin of the Chemical Society of Japan* **41**(11), 2748-53, 1968).

Shiba discloses compound VIII (figure 4, page 2750). This is encompassed by claim 1 when the substituent variables are as follows:

R^1 = -COOH

G = hydrogen

R^2 = alkylaryl; and

$Y(R^4)(Z)CH(R^3)X$ represents benzyloxycarbonyl.

Thus, the claim is anticipated.

*

Claim 1 is rejected under 35 U.S.C. §102(b) as being anticipated by Szirtes (*Journal of Medicinal Chemistry* **29**(9), 1654-8, 1986).

Szirtes discloses (table I, page 1655) compound 3a, which is the following

Z-Ica-Leu-Pro-NH_2

This is encompassed by claim 1 when the substituent variables are as follows:

G = hydrogen

R^2 = alkyl; and

R^1 = $CON(R^9)(R^{10})$, wherein R^9 and R^{10} together form heterocycloalkyl

$Y(R^4)(Z)CH(R^3)X$ represents benzyloxycarbonyl.

Thus, the claim is anticipated.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600

DAVID LUKTON
PATENT EXAMINER
GROUP 1600